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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

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(54) Title: SUBSTITUTED 5-HYDROXY-INDOLE COMPOUNDS FOR THE TREATMENT OF GLAUCOMA

(57) Abstract: The present invention provides novel compounds with 5-HT2 agonist activity, compositions containing the compounds and methods of their use to lower IOP and/or provide neuroprotection.

WO 03/051291 A3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/38625

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : C07D 209/14; A61K 31/4045
US CL : 548/504; 514/415
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 548/504; 514/415

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- A	US 5,571,833 A (KRUSE et al) 05 November 1996 (5.11.96), column 2, lines 18-52, column 11, line 17, column 12, lines 24 and 25.	2 and 5 --- 17

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
03 February 2003 (03.02.2003)	21 AUG 2003
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Sonya Wright Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/38625

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claim Nos.: 1, 3, 4, 6-16,18 and 19
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Please See Continuation Sheet

3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

Continuation of Box I Reason 2:
In these claims, the numerous variables (e.g. R1, R2, R3, R4, R5, R6, and R7) and their voluminous, complex meanings and their seemingly endless permutations and combinations, make it virtually impossible to determine the full scope and complete meaning of the claimed subject matter. As presented, the claimed subject matter cannot be regarded as being a clear and concise description for which protection is sought. Thus it is impossible to carry out a meaningful search on the same. A search will be made on the subject matter of claims 2, 5, and 17.

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(57) Abstract: The present invention provides novel compounds with 5-HT2 agonist activity, compositions containing the compounds and methods of their use to lower IOP and/or provide neuroprotection.

WO 03/051291 A2

SUBSTITUTED 5-HYDROXY-INDOLE COMPOUNDS FOR THE TREATMENT OF GLAUCOMA

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to treatment for lowering intraocular pressure and to compounds for use in such treatments. More particularly, the present invention relates to the use of compounds with serotonergic 5-HT_2 agonist activity to lower intraocular pressure (IOP), treat glaucoma, and to provide neuroprotection.

2. Description of the Related Art

The disease state referred to as glaucoma is characterized by a permanent loss of visual function due to irreversible damage to the optic nerve. The several morphologically or functionally distinct types of glaucoma are typically characterized by elevated IOP, which is considered to be causally related to the pathological course of the disease. Ocular hypertension is a condition wherein intraocular pressure is elevated but no apparent loss of visual function has occurred; such patients are considered to be a high risk for the eventual development of the visual loss associated with glaucoma. Some patients with glaucomatous field loss have relatively low intraocular pressures. These so called normotension or low tension glaucoma patients can also benefit from agents that lower and control IOP. If glaucoma or ocular hypertension is detected early and treated promptly with medications that effectively reduce elevated intraocular pressure, loss of visual function or its progressive deterioration can generally be ameliorated. Drug therapies that have proven to be effective for the reduction of intraocular pressure include both agents that decrease aqueous humor production and agents that increase the outflow facility.

Such therapies are in general administered by one of two possible routes, topically (direct application to the eye) or orally.

There are some individuals who do not respond well when treated with certain existing glaucoma therapies. There is, therefore, a need for other topical therapeutic agents that control IOP.

Serotonin (5-hydroxy tryptamine; 5-HT) is an endogenous biogenic amine with a well defined neurotransmitter function in many tissues of the body including the eye [Zifa and Fillion 1992; Hoyer *et al.* 1994; Tobin *et al.* 1988].

5-HT is known to interact with at least seven major 5-HT receptors (5-HT_1 – 5-HT_7), and additional subtypes within these families, to initiate intracellular biochemical events such as stimulation of second messengers (e.g. cAMP, inositol trisphosphate) eventually leading to the final biological response, for example, tissue contraction or hormone release, etc. [Hoyer *et al.* 1994; Martin *et al.* 1998]. Receptor subtypes within the 5-HT_1 family are negatively coupled to adenylyl cyclase (AC) and cause inhibition of cAMP production, while 5-HT_4, 5-HT_6, and 5-HT_7 receptors are positively coupled to AC and thus stimulate cAMP production when activated by 5-HT [Martin *et al.* 1998]. The receptors in the 5-HT_2 family are positively coupled to phospholipase C (PLC) and thus generate inositol phosphates and mobilize intracellular calcium when activated to mediate the effects of 5-HT. The 5-HT_3 receptor is unique in that it couples to an ion channel which gates sodium, potassium, and calcium [Hoyer *et al.* 1994].

The human and animal 5-HT_7 receptor has only recently been cloned, expressed, and shown to be present in various brain areas and peripheral tissues [Eglen *et al.* 1997]. Recent studies have shown there to be four splice variants of the 5-HT_7 receptor [Heidmann *et al.* 1997]. It has been proposed that the 5-HT_7 receptor may be involved in the pathophysiology of sleep disorders, depression, and other psychiatric disorders [Eglen *et al.* 1997]. In the periphery, stimulation of 5-HT_7 receptors results in relaxation of blood vessels and hence vasodilation [Eglen *et al.* 1997].

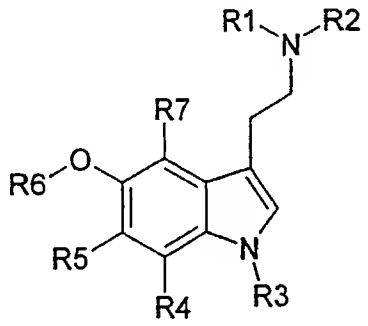
Known compounds exhibiting 5-HT_2 agonist activity have typically been designed to treat numerous central nervous system (CNS)-related conditions, particularly the treatment of obesity and depression, by activation of 5-HT_{2C} receptors. Thus, one desired property of known 5-HT_2 agonist compounds is that they easily penetrate the blood brain barrier. Compounds that readily penetrate the blood-brain-barrier by passive diffusion are generally lipophilic molecules, which do not contain polar functional groups that might impede this diffusion.

To treat ocular diseases, it is desirable to administer compositions orally or topically that will remain in the ocular tissues and not cross the blood brain barrier to enter the CNS. What are needed are 5-HT_2 agonist compounds that are useful in the treatment of ocular diseases characterized by an elevated intraocular pressure, the treatment of glaucoma, and also provide neuroprotection to the retina. Such compounds would not have a high propensity to cross the blood brain barrier.

SUMMARY OF THE INVENTION

The present invention overcomes these and other drawbacks of the prior art by providing compounds having 5-HT_2 agonist activity that do not cross the blood brain barrier. More specifically, the present invention provides compounds having the following general formula:

Formula I:



wherein R^1 and R^2 are C_{1-6}alkyl or R^1 and R^2 can together complete a four to seven-membered heterocyclic ring which may contain a second heteroatom selected from O, S, NH, NC_{1-4}alkyl; R^3 is hydrogen, C_{1-4}alkyl; R^4, R^5, and R^7 are independently selected from hydrogen, C_{1-4}alkyl, halogen, nitrile, C_{1-6}alkylthiol, trifluoromethyl; R^6 is hydrogen, or $C(=O)C_{1-8}$alkyl, which may be branched or unbranched. The compound, bufotenine, discussed hereinbelow, is not within the scope of the compounds of the invention. In preferred embodiments, R^1 and R^2 are methyl, R^3 and R^6 are hydrogen and R^4, R^5 and R^7 are hydrogen or halogen. In more preferred embodiments, R^6 is a branched $C(=O)C_{1-8}$alkyl. Most preferably, R^6 is hydrogen or valproic acid.

In another aspect, the present invention provides compositions containing the compounds described above in a pharmaceutically acceptable excipient. The compositions

of the invention may also include bufotenine in a pharmaceutically acceptable excipient. The compositions are most preferably in the form of topical ophthalmic formulations for delivery to the eye. The compounds of the invention may be combined with ophthalmologically acceptable preservatives, surfactants, viscosity enhancers, penetration enhancers, buffers, sodium chloride, and water to form an aqueous, sterile ophthalmic suspension or solution to form the compositions of the invention.

The compositions of the invention are preferably formulated as topical ophthalmic suspensions or solutions, with a pH of about 5 to 8. The compounds of the invention as described above will normally be contained in these formulations in an amount .01% to 5% by weight, but preferably in an amount of .25% to 2% by weight. Thus, for topical presentation 1 to 2 drops of these formulations would be delivered to the surface of the eye 1 to 4 times per day according to the routine discretion of a skilled clinician.

The present invention further provides a method of lowering intraocular pressure in a mammal by administering to a patient in need thereof a therapeutically effective amount of a composition comprising a compound having the structure as described above. The methods of the invention may include the use of compositions containing bufotenine.In preferred embodiments, the composition can be administered systemically or locally to the eye (e.g., topically, intracamerally, or via an implant).

DETAILED DESCRIPTION PREFERRED EMBODIMENTS

Unexpectedly, it has been found that serotonergic compounds which possess agonist activity at 5-HT_2 receptors effectively lower and control elevated IOP and

glaucoma. In addition, the compounds provide neuroprotective activity and are useful for treating persons suffering from ocular diseases associated with neuronal cell death.

It has been found that serotonergic compounds which possess agonist activity at 5-HT_2 receptors effectively lower and control normal and elevated IOP and are useful for treating glaucoma, see commonly owned co-pending application, PCT/US99/19888.

Compounds that act as agonists at 5-HT_2 receptors are known and have shown a variety of utilities, primarily for disorders or conditions associated with the central nervous system (CNS). U.S. Patent 5,494,928 discloses certain 2-(indol-1-yl)-ethylamine derivatives that are 5-HT_{2C} agonists for the treatment of obsessive compulsive disorder and other CNS derived personality disorders. U.S. Patent 5,571,833 discloses tryptamine derivatives that are 5-HT_2 agonists for the treatment of portal hypertension and migraine. U.S. Patent 5,874,477 discloses a method for treating malaria using 5-$HT_{2A/2C}$ agonists. U.S. Patent 5,902,815 discloses the use of 5-HT_{2A} agonists to prevent adverse effects of NMDA receptor hypo-function. WO 98/31354A2 discloses 5-HT_{2B} agonists for the treatment of depression and other CNS conditions. Agonist response at the 5-HT_{2A} receptor is reported to be the primary activity responsible for hallucinogenic activity, with some lesser involvement of the 5-HT_{2C} receptor possible [Fiorella *et al* 1995].

A specific disclosure in co-pending application PCT/US99/19888 relates to certain substituted α-methyltryptamines which are effective agents for lowering intraocular pressure in mammals. However, when a phenolic moiety is included in this substitution, e.g. a hydroxyl group at indole ring position five, such compounds can be particularly sensitive to oxidation reactions well known to occur with phenolic compounds in general,

including hydroxytryptamines [Hela *et al.* 1999; Wrona *et al.* 1998; Wrona *et al.* 1987; Wrona *et al.* 1988], which are of particular relevance to the present application. Protection of such hydroxy substituted tryptamines from oxidation can be accomplished by derivatization of the aryl hydroxy group to provide a suitable ester, carbamate, or carbonate. Though the ester, carbamate, or carbonate derivatives do not themselves possess a high affinity for the above mentioned receptors, they do have utility in the treatment of glaucoma since suitably protected phenols can be cleaved in vivo either by chemical hydrolysis or through the action of tissue esterases, thereby delivering the desired therapeutic agent, that is, the desired hydroxytryptamine compound in the present case. The concept of utilizing such derivatized phenolic compounds as chemical delivery agents is well known in the art [Lee *et al.* 1992; Bodor *et al.* 1984].

It has been found that 5-methoxy-*N,N*-dimethyl-tryptamine - (5-MeO-DMT) has a high affinity for and potent efficacy at both the 5-HT_2 and 5-HT_{1A} receptors coupled with an IOP lowering effect (WO 00/16761). Unfortunately, this compound is also known to exhibit hallucinogenic activity [A. T. Shulgin *et al.* 1978]. Serotonin is a very polar molecule, which does not readily cross the blood-brain barrier due, at least in part, to its low lipid solubility. Similarly, *N,N*-dimethyl-serotonin [*N,N*-dimethyl-5-HT or bufotenine] [$DC_{7.4}$ 0.15] would be expected to have a low propensity to penetrate the blood-brain barrier relative to 5-MeO-DMT [$DC_{7.4}$ 3.3]. In fact, it has been demonstrated that *O*-acetyl bufotenine does readily cross the blood-brain barrier and is rapidly hydrolyzed to bufotenine in the brain, thus, providing a method of delivery of bufotenine to the brain (Gessner *et al.* 1968; Gessner *et al.* 1975).

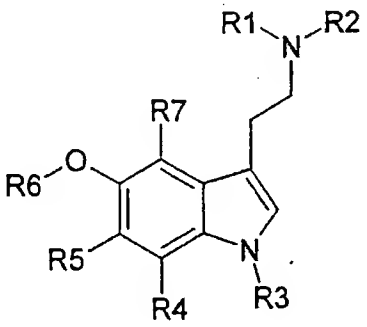
Bufotenine has been reported to ellicit hallucinations in man. This observation is based on a single small study (Fabing *et al.* 1956) (four males), which has been broadly refuted based on other interpretations of the original observations (Fischer 1968) and subsequent studies. It has been reported that up to 20 mg of bufotenine i.v., did not produce hallucinations in humans (Turner 1959).

Though bufotenine has a low propensity to cross the blood-brain barrier, if it does gain entry to the brain, e.g. via a prodrug modification, such as *O*-acetyl bufotenine, it would be anticipated based on its pharmacological profile, to have a propensity to ellicit marked central nervous system effects similar to 5-MeO-DMT (McBride 2000; Gessner *et al.* 1962).

Bufotenine has not been reported to have IOP lowering activity, or any other activity in the eyes. The present inventors have discovered that bufotenine effectively lowers IOP in a lasered monkey model of ocular hypertension. Furthermore, bufotenine has good affinity and acceptable agonist activity at both the 5-HT_{2A} and 5-HT_{1A} receptors. The observed reduction in IOP following topical ocular administration of bufotenine, a molecule known to have a very low level of transport to the brain, illustrates that ready access to the CNS is not a requirement for achieving a significant reduction of IOP in the monkey with a 5-HT_2 receptor agonist. This is a distinct advantage with regard to a potential absence of significant CNS related side effects in man.

The present inventors have discovered that compounds having the general formula (Formula I) below are useful in treating patients with glaucoma, for lowering intraocular pressure (IOP), and/or to provide neuroprotective activity for retinal ganglion cells.

Formula I



In preferred compounds described by Formula I, R^1 and R^2 are C_{1-6}alkyl or R^1 and R^2 can together complete a four to seven-membered heterocyclic ring which may contain a second heteroatom selected from O, S, NH, NC_{1-4}alkyl; R^3 is hydrogen, C_{1-4}alkyl; R^4, R^5, and R^7 are independently selected from hydrogen, C_{1-4}alkyl, halogen, nitrile, C_{1-6}alkylthiol, trifluoromethyl; R^6 is hydrogen or $C(=O)C_{1-8}$alkyl, which may be branched or unbranched, provided that the compound is not bufotenine. The most preferred compounds are those where R^1 and R^2 are methyl; R^3, R^4, R^6 are hydrogen, R^5, R^7 are hydrogen, halogen, or methyl. In one particularly preferred embodiment, R^6 is a branched $C(=O)C_{1-8}$ alkyl. One preferred branched $C(=O)C_{1-8}$alkyl is valproic acid. Valproic acid is a clinically proven anti-epileptic and neuroprotective agent. The presence of valproic acid at the 5-hydroxyl terminus of the compounds of the invention would enable the compounds to cross the cornea after topical instillation. The compound would either be hydrolyzed or remain intact to lower IOP and reach the back of the eye to protect the retina.

It is recognized that compounds of Formula I can contain one or more chiral centers. This invention contemplates all enantiomers, diastereomers and, mixtures thereof.

In the above definitions, the total number of carbon atoms in a substituent group is indicated by the Ci-j prefix where the numbers i and j define the number of carbon atoms; this definition includes straight chain, branched chain, and cyclic alkyl or (cyclic alkyl)alkyl groups.

It is important to recognize that a substituent may be present either singly or multiply when incorporated into the indicated structural unit. For example, the substituent halogen, which means fluorine, chlorine, bromine, or iodine, would indicate that the unit to which it is attached may be substituted with one or more halogen atoms, which may be the same or different.

The compounds of the invention can be made using known synthetic techniques. For example, preparations of fluoro derivatives, particularly where R^5 or R^7 are fluoro, follow the reported synthesis for related alkoxy compounds (Blair *et al.* 2000; Laban *et al.* 2001).

The compounds of the invention can be administered systemically or locally to the eye (e.g., topically, intracamerally, or via an implant). The compounds are preferably incorporated into topical ophthalmic formulations for delivery to the eye. The compounds may be combined with ophthalmologically acceptable preservatives, surfactants, viscosity

enhancers, penetration enhancers, buffers, sodium chloride, and water to form an aqueous, sterile ophthalmic suspension or solution. Ophthalmic solution formulations may be prepared by dissolving a compound in a physiologically acceptable isotonic aqueous buffer. Further, the ophthalmic solution may include an ophthalmologically acceptable surfactant to assist in dissolving the compound. Additionally, the ophthalmic solution may contain an agent to increase viscosity, such as, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose, methylcellulose, polyvinylpyrrolidone, or the like, to improve the retention of the formulation in the conjunctival sac. Gelling agents can also be used, including, but not limited to, gellan and xanthan gum. In order to prepare sterile ophthalmic ointment formulations, the active ingredient is combined with a preservative in an appropriate vehicle, such as, mineral oil, liquid lanolin, or white petrolatum. Sterile ophthalmic gel formulations may be prepared by suspending the active ingredient in a hydrophilic base prepared from the combination of, for example, carbopol-940, or the like, according to the published formulations for analogous ophthalmic preparations; preservatives and tonicity agents can be incorporated.

The compounds of the invention are preferably formulated as topical ophthalmic suspensions or solutions, with a pH of about 5 to 8. The compounds will normally be contained in these formulations in an amount .01% to 5% by weight, but preferably in an amount of .25% to 2% by weight. Thus, for topical presentation 1 to 2 drops of these formulations would be delivered to the surface of the eye 1 to 4 times per day according to the routine discretion of a skilled clinician.

The compounds can also be used in combination with other IOP lowering agents, such as, but not limited to, β-blockers, prostaglandins, carbonic anhydrase inhibitors, α-$_2$ agonists and miotics. The compounds can also be used in combination with other agents useful for treating glaucoma, such as, but not limited to, calcium channel blockers and NMDA antagonists. These agents may be administered topically, but usually systemically.

The following examples are included to demonstrate preferred embodiments of the invention. It should be appreciated by those of skill in the art that the techniques disclosed in the examples which follow represent techniques discovered by the inventor to function well in the practice of the invention, and thus can be considered to constitute preferred modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.

Example 1

Bufotenine was purchased as the oxylate salt from BioSynth International and transformed by the inventors to the fumarate salt. This salt conversion was critical in order to achieve a meaningful evaluation of the compound during *in vivo* tests in the monkey. It has been observed that a compound, which is not well tolerated by rabbits during a general ocular safety evaluation will also generally not be well tolerated by monkeys when administered topically to the eye, thereby not providing a reliable evaluation of the activity of the test compound in this model. Oxalic acid or oxalate salts

are typically not well tolerated by rabbits when evaluated in such studies, and hence it is not acceptable to potentially compromise the monkeys by exposure to oxalate salts.

To further assess the CNS activity of bufotenine, the inventors evaluated its response in a mouse head-twitch assay. A positive response in this assay is well documented to be initiated by activation of central 5-HT_{2A} receptors. Following subcutaneous dosing (1-10 mg/kg), bufotenine did not initiate any observable head-twitch responses in the test group of mice. However, when DOI, a selective 5-HT_2 agonist which is known to readily enter the brain, was dosed in a similar manner a significant positive response was observed within the test group of mice. The interpolated effective dose of DOI that produced a mean of five twitches (ED_5) was determined to be 0.1 mg/kg. These observations further support the lack of entry of bufotenine into the brain.

All of the compositions and/or methods disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure. While the compositions and methods of this invention have been described in terms of preferred embodiments, it will be apparent to those of skill in the art that variations may be applied to the compositions and/or methods and in the steps or in the sequence of steps of the method described herein without departing from the concept, spirit and scope of the invention. More specifically, it will be apparent that certain agents which are both chemically and structurally related may be substituted for the agents described herein to achieve similar results. All such substitutions and modifications apparent to those skilled in the art are deemed to be within the spirit, scope and concept of the invention as defined by the appended claims.

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The following references, to the extent that they provide exemplary procedural or other details supplementary to those set forth herein, are specifically incorporated herein by reference.

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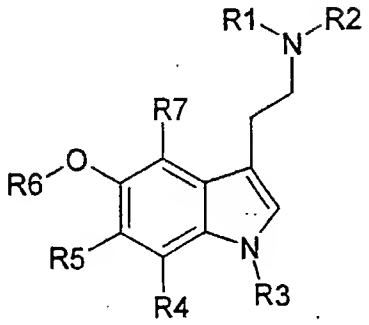
We Claim:

1. A compound having the structure as follows:

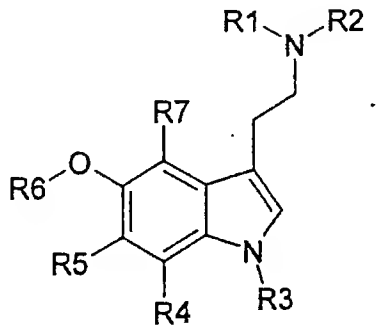


wherein R^1 and R^2 are C_{1-6}alkyl or R^1 and R^2 can together complete a four to seven-membered heterocyclic ring which may contain a second heteroatom selected from O, S, NH, NC_{1-4}alkyl; R^3 is hydrogen, C_{1-4}alkyl; R^4, R^5, and R^7 are independently selected from hydrogen, C_{1-4}alkyl, halogen, nitrile, C_{1-6}alkylthiol, trifluoromethyl; R^6 is hydrogen, or $C(=O)C_{1-8}$alkyl, which may be branched or unbranched, provided that the compound is not bufotenine.

2. The compound of claim 1, wherein R^1 and R^2 are methyl, R^3 and R^6 are hydrogen and R^4, R^5 and R^7 are hydrogen or halogen.

3. The compound of claim 1, wherein R^6 is valproic acid.

4. A composition comprising at least one compound having the structure as follows and a pharmaceutically acceptable excipient:



wherein R^1 and R^2 are C_{1-6}alkyl or R^1 and R^2 can together complete a four to seven-membered heterocyclic ring which may contain a second heteroatom selected from O, S, NH, NC_{1-4}alkyl; R^3 is hydrogen, C_{1-4}alkyl; R^4, R^5, and R^7 are independently selected from hydrogen, C_{1-4}alkyl, halogen, nitrile, C_{1-6}alkylthiol, trifluoromethyl; R^6 is hydrogen, or $C(=O)C_{1-8}$alkyl, which may be branched or unbranched.

5. The compound of claim 4, wherein R^1 and R^2 are methyl, R^3 and R^6 are hydrogen and R^4, R^5 and R^7 are hydrogen or halogen.

6. The composition of claim 4, further comprising ophthalmologically acceptable preservatives.

7. The composition of claim 4, further comprising ophthalmologically acceptable surfactants.

8. The composition of claim 4, further comprising an agent to increase viscosity.

9. The composition of claim 9, wherein the agent is selected from the group consisting of hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose, methylcellulose, and polyvinylpyrrolidone.

10. The composition of claim 4, further comprising ophthalmologically acceptable preservatives, ophthalmologically acceptable surfactants and at least one agent to increase viscosity.

11. The composition of claim 4, further defined as a topical ophthalmic suspension or solution having a pH of about 5 to about 8.

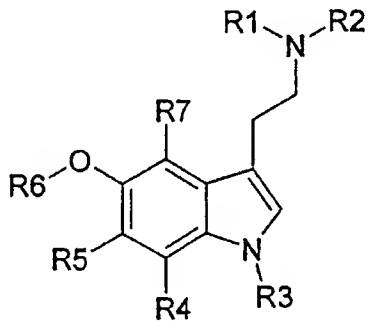
12. The composition of claim 12, wherein the concentration of the compound is from .01% to 5% by weight.

13. The composition of claim 13, wherein the composition of the compound is from .25% to 2% by weight.

14. The composition of claim 4, further comprising at least one agent selected from the group consisting of β-blockers, prostaglandins, carbonic anhydrase inhibitors, α-$_2$ agonists and miotics.

15. The composition of claim 4, further comprising at least one agent selected from the group consisting of calcium channel blockers and NMDA antagonists.

16. A method of lowering intraocular pressure in a mammal, said method comprising administering to a patient in need thereof a therapeutically effective amount of a composition comprising a compound having the structure as follows:



wherein R^1 and R^2 are C_{1-6}alkyl or R^1 and R^2 can together complete a four to seven-membered heterocyclic ring which may contain a second heteroatom selected from O, S, NH, NC_{1-4}alkyl; R^3 is hydrogen, C_{1-4}alkyl; R^4, R^5, and R^7 are independently selected from hydrogen, C_{1-4}alkyl, halogen, nitrile, C_{1-6}alkylthiol, trifluoromethyl; R^6 is hydrogen, or $C(=O)C_{1-8}$alkyl, which may be branched or unbranched.

17. The method of claim 16, wherein R^1 and R^2 are methyl, R^3 and R^6 are hydrogen and R^4, R^5 and R^7 are hydrogen or halogen.

18. The method of claim 17, wherein the composition is in the form of a topical ophthalmic suspension or solution.

19. The method of claim 17, wherein the composition is administered topically to the eye.

5